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EXAMINER	
REDDIG, PETER J	

ART UNIT	PAPER NUMBER
1642	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DocketingDept@young-thompson.com

Office Action Summary	Application No.	Applicant(s)	
	10/530,488	TJOTTA, ENOK	
	Examiner	Art Unit	
	Peter J. Reddig	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/17/2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28, 30-34, 37-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28,30-34,37-41,44 and 46-61* is/are rejected.

7)☒ Claim(s) *32,39,42,43,45,48,51 and 60* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 December 2008* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn. The amendment filed 12/17/2008 has been entered. Additionally, the Restriction requirement of 5/8/2008 is withdrawn. Claims 28, 30-34, 37-61 are currently under consideration.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 40 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons set forth with regard to "potential toxins" in section 6 of the Office Action of 9/17/2008.

Applicant argues that potential toxins is a common expression to a toxin which are not toxic in healthy peoples, but unusual high concentrations, a special constitution, metabolism or disease may make intake of such potential toxins toxic. Intake of such compounds may occur through food, health food, drugs, air, water, cosmetics, and pollutions or by direct contact.

Applicants' arguments have been considered, but have not been found persuasive. As indicated by Applicant's arguments what is covered by the term "potential toxin" is variable and the specification provides no clear limit or standard as to when something is or is not a potential toxin. It is noted that Section 2173.05(b) of the MPEP states that a claim may be rendered

indefinite by reference to an object that is variable. Thus, given that a "potential toxin" can vary depending on who or what it is used, the term is indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 28, 30-32, 34, 38-41, 44, 46-53, 59, 60 and 61 remain or are rejected under 35 U.S.C. 102(b) as being anticipated by Prechel et al. (Cancer Letters, 1995, 92: 235:242) as evidenced by Car et al. (Toxicologic Pathology, 1999, Vol. 24:58-63) essentially for the reasons set forth in section 8 of the Office Action of 9/17/2008, which is set forth below.

Prechel et al. teach testing the effect *in vivo* effect of IL-12 on colony formation of myeloid cells in mice that had been immunized with Lewis lung carcinoma LLC-LN7 tumor cells with IL-12, which stimulates the growth of myeloid colonies, see p. 237-2nd col. figure 1, and Table 1. Prechel et al. teach testing the effect of IL-12 on colony formation of myleoid cells in vitro by seeding bone marrow and spleen cells in 1 ml of semisolid RPMI-1640 medium supplemented with 20% FBS and 0.3% agar, see p.236, p. 237-2nd col. and Fig. 2. This colony forming assay would clone and select cells for cells that grow in the presence of IL-12 that are from mice immunized with LLC-LN7 tumor cells. Prechel et al. teach injecting mice with tumor cell, treating with IL-12 and determining the effect of palpable local tumor size and the formation of metastatic lung nodules, see p. 240 and Fig. 6.

It is noted that, given the indefinite nature of the term "liberation of cells", it is assumed for examination purposes that "liberation of cells" is the formation of tumor metastasis.

Car et al. teach that IL-12 is a heterodimeric cytokine produced by several types of cells that is used as a drug, but also has toxic effects, see p. 58. Thus, IL-12, is drug, toxin, and a component of a physiological process.

Although the reference does not specifically state that they determined the effect of IL-12 on migration, given that is well known in the art that metastases involves the migration of cells from one location in the body to another location in the body, the claimed method appears to be the same as the prior art method, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the method of the prior art does not possess the same material, structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is

on the applicant to prove that the claimed method is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA).

Applicant argues that PRECHEL et al. evaluated the effects of IL-12 on immune parameters and tumor progression in an animal tumor model in which tumor production of GM-CSF leads to myelopoietic stimulation giving rise to an increased number of immune suppressive GM- progenitor cells that suppress anti-tumor immune responses. IL-12 augmented the myelopoietic stimulation that is induced by the progressively growing tumor, although it diminished the proliferative potential of the myeloid progenitor cells. The presence of GM-CSF-induced immune suppressor cells in the bone marrow, spleen and tumor was not reduced by IL-12. T cell functions in tumor bearers were suppressed and this generally was not overcome by IL-12 treatment. While IL-I2 enhanced tumor-specific cytolytic activity in the draining lymph nodes, there were no effects on the frequency of intratumoral CD8+ T-cells, on the growth of s.c. tumors, or on the formation of metastases.

Applicant argues that in PRECHEL et al., there is no effect of IL-12 on metastases, and the article does not describe a specific affection of clonal growth that is different for collocated and scattered identical cells.

Applicant argues that in contrast, the immune modulating effect of the specific clonal inhibitors of the present invention is a side- effect that is not wanted in connection with treatment of tumors or viral infections and is probably significant only for primary immune reactions. The effect on virus production is also linked to the specific nature of the inhibition of clonal growth since the metabolism of collocated identical cells is not significantly affected. Only marginal effects may be present.

Applicant argues that therefore, PRECHEL et al. fail to consider specific clonal inhibitors or enhancers, and IL-12 has no effect on formation of metastases. Therefore, this PRECHEL et al. includes no relevant counter-arguments against my patent application.

Applicant argues that the Office Action refers to CAR et al. as evidence of IL-12 is a heterodimeric cytokine produced by several types of cells but also has toxic effects.

Applicant argues that however, CAR et al. conclude that recombinant murine interleukin (IL) 12 (rmIL-12) exhibits antitumor, antiviral, and antimicrobial activities and can modify allergic inflammatory reactions in animal models. Recombinant human IL-12 (rhlL-12) is currently in clinical trials for treatment of cancer, asthma, and viral hepatitis.

Applicant argues that the specific clonal inhibitors, however, do not have general anti-tumor, antiviral, antimicrobial activities. Treatment with specific clonal inhibitors is expected only to inhibit activity in identical cells that were sparsely seeded in cultures or sparsely distributed among other cells in the body. The article does not describe an activity of IL-12 and related substances that are confined to only scarcely distributed identical cells in cultures or animals.

Applicant argues that therefore, the conclusion must be the same for both PRECHEL et al. and CAR et al.

Applicant argues that PRECHEL et al. thus fail to consider specific clonal inhibitors or enhancers and thus fails to anticipate a claimed embodiment of the present invention.

Applicant's arguments have been considered, but have not been found persuasive. Applicants are arguing that the clonal inhibitors must have specific properties, which are argued to be not associated with IL-12. However, claims 28, 29-32, 34, 38-41, 44, 46, and 61 are

testing/selecting methods for determining if an agent inhibits or stimulates clonal growth and thus the agents tested by the methods need not have the activity being sought or the activity of the compounds taught in the specification. The claimed methods are for determining if the clonal inhibitory or stimulatory activity is present and/or making a selection based on the results of the tests, which can be positive or negative. Thus Prechel et al. anticipates for the reasons previously set forth.

Additionally, IL-12 is encompassed by the broadly claimed analogues of 48, 51, and 60. Furthermore, with regard to claims 47, 50, and 59, IL-12 functions to stimulate colony formation, while reducing cell proliferation in bone marrow and spleen in vivo. See Fig. 1 and 2. Thus, at effective does IL-12 has the ability to either stimulate or inhibit different aspects of clonal cell growth, i.e. colony formation and proliferation. Furthermore, the clonal mitotic inhibitor or stimulator of claims 47, 50 and 59 are products identified by a process and the patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claim. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). Thus, the clonal mitotic inhibitor or stimulator used in claims 47, 50 and 59 need not be selected by the method of claim 28. Thus, the serum, which contains serum factors, in the culture media used to grow the LLC-LN7 tumor cells, is a clonal mitotic stimulator that stimulates clonal growth of the cultured cells. See p. 236-1st col.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. Claim 33 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Prechel et al. (Cancer Letters, 1995, 92: 235:242), in view of De Asua et al. (Proc. Natl. Acad. Sci USA, 1973, 70:1388-13920) and in view of Kamei H. (Cell Biol. Int. Rep. Jan. 1987, 11 (1): 35-41) for the reasons set forth in section 9 of the Office Action of 9/17/2008, which are set forth below.

Claim 33 is drawn to the method according to claim 29, wherein the cells are selected from the group consisting of BHK21/c13, and BHK21/C13 cells transformed with polyoma virus.

Prechel et al. teach as set for above, but do not teach using BHK21/c13, and BHK21/C13 cells transformed with polyoma virus .

De Asua et al. teach testing the effect of insulin and cAMP on BHK21/13 agar colony formation, see Abstract and Table 1.

Kamei H. teaches that the BHK21/13 cells of De Asua cells are BHK21/c13 cells, see Introduction p. 35. Kamei et al. also teaches using a BHK21/c13 clone to study the effects of retinoic acid on anchorage independent growth of the BHK21/c13 clone cells, see Abstract..

It would have been *prima facie* obvious at the time the invention was made to use the BHK21/c13 cell agar colon assay of De Asua in combination with the method of Prechel et al. to determine the effect of IL-12 on BHK21/c13 cell anchorage independent growth. One of skill in the art would have been motivated to use BHK21/c13 cell cells to determine the breadth of IL-12 activity on different cell types. As the skill in the art is high, one of skill in the art would have had a reasonable expectation of success of using BHK21/c13 cells as they were a well known model for assaying the effects of agents *in vitro* cell studies of clonal cell growth.

Applicant argues that PRECHEL et al. also fail to be a basis for an assertion of prima facie unpatentability.

Applicant argues that the Official Action acknowledged that PRECHEL et al. fail to teach using BHK21/cI3 and BHK21/CI3 cells transformed with polyoma virus. The Official Action turns to DE ASUA and KAMEI.

Applicant argues that the DE ASUA et al. reference shows that BHK 21/13 fibroblasts grown in the presence of insulin show some characteristics of a transformed strain. The effect is shown both in agar and when grown on surface.

Applicant argues that in the experiments described in the present invention, insulin induces growth of normal cells in soft agar medium. Then specific clonal inhibitors can inhibit these cells, but only when they were sparsely distributed in the culture. This is possible since insulin stimulates both collocated cells and sparsely seeded cells in culture.

Applicant argues that therefore, the conclusion must be the same as for PRECHEL et al. and CAR et al., and DE ASUA et al. fail to consider specific clonal inhibitors or enhancers and is not a relevant counter-argument against my patent application.

Applicant's arguments have been considered, but have not been found persuasive because Applicant is arguing limitations that are not found in the claim. The claims are a method for testing and selecting an agent to determine whether said agent inhibits or stimulates clonal growth. The claimed method is trying to identify these inhibitors or stimulators. Thus, the claims are not limited to using an agent that has activity on clonal growth. Thus, given that Prechel et al. and De Asua et al. teach the clonal tests as previously set forth, it would have been obvious to

use the BHK21/C13 of DeAsua et al. in the method of Prechel et al. for the reasons previously set forth.

Applicant argues that KAMEI focuses on a test that may show inhibition of anchorage independent growth of transformed cells that may be suppressed by chemicals as retinoic acid. Anchorage independent growth is a growth pattern that transformed cells may show when growing on a surface, also called criss-cross appearance.

Applicant argues that there is a connection between this appearance and the ability that such transformed cell lines have when growing in soft agar: they can form colonies in an agar where the untransformed parent cell line is unable to form colonies.

Applicant argues that therefore, what this test does is performed to select compounds with the ability to revert temporarily or may be more permanently, the transformed phenotype.

Applicant argues that moreover, not all fetal bovine sera (FBS) supported the suppression of anchorage independent growth of retinoic acid, and insulin enhanced the anchorage independent growth in both types of sera even in the presence of retinoic acid.

Applicant argues that Kamei's article may have been a logical counter argument against the present invention if the content of claim 28 was only: "A method for testing and selecting an agent to determine whether said agent inhibits or stimulates clonal growth." Applicant argues that but there is more:

Claim 28, b) "testing the effect those different degrees of local collocation of cells has on the effect of said agent on cloning." This is elaborated in claims 48-52.

Applicant argues that the selection of agents by the test described in the specification is based on the specific inhibition or specific stimulation of clonal growth of cells either seeded

sparsely in (agar) culture or transplanted as single cells sufficiently diluted and scattered in tissues. No such inhibition or stimulation of growth of single cells occurs if these cells are locally congregated (collocated) either in culture or in the animal, it is important to be aware that other cells in the animal do not affect the degree of collocation of the transplanted identical cells and thus not the specific inhibition or stimulation of the transplanted cells. It is only the distance between the identical transplanted single cells that counts, not the number of other cells in the body of the animal in the same area.

Applicant argues that therefore, development of local infiltration or metastases as well as growth of clones resistant to ongoing treatment will be inhibited or come to a stop by the specific clonal inhibitors detected and selected by the test.

Applicant argues that the conclusion is that Kamei's article does not consider specific clonal inhibitors or enhancers and is not relevant to the present invention.

Applicant's arguments have been considered, but have not been found persuasive because, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. Applicant has argued and discussed the Kamei reference individually without clearly addressing the combined teachings. It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which made up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The claims are a method for

testing and selecting an agent to determine whether said agent inhibits or stimulates clonal growth. The claimed method is trying to identify these inhibitors or stimulators. The claims are not limited to using an agent that has activity on clonal growth. Thus, given that Prechel et al., De Asua et al and Kamei teach the clonal tests as previously set forth, it would have been obvious to use the BHK21/C13 of DeAsua et al. or Kamei in the method of Prechel et al. for the reasons previously set forth.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., seeded sparsely in (agar) culture or transplanted as single cells sufficiently diluted and scattered in tissues) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Thus, Applicant's arguments have not been found persuasive and the rejection is maintained.

5. Claim 37 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Prechel et al. (Cancer Letters, 1995, 92: 235:242) in view of US Pat. No. 4,744, 985 (Tami et al. May 17, 1988) for the reasons set forth in section 10 of the Office Action of 9/17/2008, which are set forth below.

Claim 37 is drawn to the method according to claim 36, wherein said tumor cells are transplanted Ehrlich carcinoma cells.

Prechel et al. teach as set for above, but do not teach tumor cells are transplanted Ehrlich carcinoma cells.

US Pat. No. 4,744, 985 teaches using Ehrlich tumor cells transplanted intraperitoneally or into the armpits of mice to determine the antitumor activity of bacterial extracts, see cols.20-24.

It would have been *prima facie* obvious at the time the invention was made to use the Ehrlich tumor cells of US Pat. No. 4,744, 985 in the examination of tumor growth/metastasis

method of Prechel et al. to determine the effect of IL-12 on transplanted Ehrlich tumor cell growth and metastasis. One of skill in the art would have been motivated to use Ehrlich tumor cells to determine the breadth of IL-12 activity on different tumor types. As the skill in the art is high, one of skill in the art would have had a reasonable expectation of success of using Ehrlich tumor cells as they were a well known model of tumor formation.

Applicant argues that regarding TAMAI et al., the Abstract sets forth that substances having carcinostatic and immunostimulating activity, which are obtained from a culture or its supernatant fluid prepared by culturing bacteria belonging to the Fusobacterium genus. The substances are useful for the treatment of cancerous diseases in lower warm-blooded animals. This disclosure concerns such substances and a process for preparing the same and a carcinostatic agent containing the same.

Applicant argue that Column 1, third paragraph of TAMAI et al. states: ". . .a specific component obtained from the supernatant fluid has a carcinostatic activity in lower warm-blooded animals; that said component has substantially no effect of inhibiting the formation of a colony of cancer cells in a colony forming assay method, and has not a carcinostatic activity by killing the cancer cells."

Applicant argues that TAMAI et al. teaches that the formation of colonies is not inhibited by these substances in a colony forming assay. That is completely different from compounds selected by my method described in my patent application where the inhibition is specifically directed against clonal growth of scarcely distributed identical cells.

Applicant argues that table 2 of TOMAI et al. indicates that: all fractions from TF-100 to TF-150 had an immune-stimulating activity.

Applicant argues that in contrast, the selected specific clonal inhibitors of the present invention do not stimulate immunity. The primary immune reaction is, on the other hand,

expected to be significantly suppressed. Table 2 indicates that: all fractions from TF-100 to TF-150 inhibited Ehrlich solid tumor. This effect of TF-I 10 and TF-I 20 is not described.

Applicant argues that it is thus noted that the best specific clonal inhibitor 4-OH-OPB stimulated growth of Ehrlich solid tumor. Therefore, these fractions have nothing in common with the inhibitor of the present invention and there is no reason to believe that the specific clonal stimulators detected by my method would inhibit Ehrlich solid tumors. The effects of the extracts of Tamai et al. are not thus in accordance with the effects of specific clonal inhibitors or stimulators detected by the method of the present invention.

Applicant argues that as a result, no combination of the secondary references with PRECHEL et al. is sufficient to alleged prima facie unpatentability. Even if this unpatentabilty could be alleged, it would by dissipated by the unexpected results shown in the Examples and the drawing figures.

Applicant's arguments have been considered, but have not been found persuasive because the claims are a method for testing and selecting an agent to determine whether said agent inhibits or stimulates clonal growth. The claimed method is trying to identify these inhibitors or stimulators. Thus, the claims are not limited to using an agent that has activity on clonal growth for testing or agents recited in the specification. Thus, given that Prechel et al. and Tamei teach the clonal tests as previously set forth, it would have been obvious to use the Ehrlich tumor cells of Tamei in the method of Prechel et al. for the reasons previously set forth. Thus, Applicant's are not found persuasive and the rejection is maintained.

New Grounds of Rejection

Drawings

6. The drawings submitted 12/17/2008 are objected to because the images of 5A-D, 9C, 10, 11, and 12 are not legible. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

7. Claims 32, 39, 48, 51 and 60 are objected to because of the following informalities: There is a "u" next to "28" in claim 32. The word "Kolchicin" should be spelled "colchicine" in claims 48 and 51. The word "Sulindak" in claim 60 should be spelled "Sulindac". The word "Diclofenak" in claim 60 should be spelled "Diclofenc". There should be a comma between the words "toxins" and microbes in claim 39.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 52, 54 and 55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 52 recites the limitation "the patient" in reference to claim 51. There is insufficient antecedent basis for this limitation in the claim because claim 51 depends from claim 50 which is drawn to inhibiting "the subject". Amending the claims to both refer to patient or subject would obviate this rejection.

The term "piling up" in claim 54 is a relative term which renders the claim indefinite. The term " piling up " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The specification does not teach at what point infected cells are considered to be "piling up".

Section 2171 of the M.P.E.P. states

> *There are two separate requirements set forth in this paragraph:*
> *(A) the claims must set forth the subject matter that applicants regard as their invention; and*
> *(B) the claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant.*
>
> *The first requirement is a subjective one because it is dependent on what the applicants for a patent regard as their invention. The second requirement is an objective one because it is not dependent on the views of applicant or any particular individual, but is evaluated in the context of whether the claim is definite — i.e., whether the scope of the claim is clear to a hypothetical person possessing the ordinary level of skill in the pertinent art.*

In the instant case of "piling up", one of skill in the art could find representative examples in the art which have been defined in such terms, however, it is unclear at what point one of skill in the art would be infringing on the claims without limitations as to the metes and bounds of "piling up".

Claim 55 recites the limitation "the collocated infected cells". There is insufficient antecedent basis for this limitation in the claim because neither the antecedent portion of claim 55, claim 53, nor claim 50 from which claim 55 ultimately depends refers to collocated infected cells.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 48, 49, 51-53 and 55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inhibiting clonal cell growth or clonal cell growth in a subject, comprising: administering to the cells or subject an effective amount of a clonal mitotic inhibitor, wherein the clonal mitotic inhibitors are selected from the group consisting of 4-OH-OPB, colchicine, Ibuprofen, Naproxen, and acetyl salicylic acid, *does not* reasonably provide enablement for a method for inhibiting clonal cell growth or clonal cell growth in a subject, comprising: administering to the cells or subject an effective amount of a clonal mitotic inhibitor, wherein the clonal mitotic inhibitors are selected from the group consisting of p-hydroxy-azobenzene, 2-Butyl-2-hydroxy-N-(4- hydroxy-phenyl)-N'-phenyl malonamide, 1,2-diphenyl-4-hydroxy-4-[2-(phenylsulfinyl)ethyl]-3,5-pyrazolidinedione, analogues thereof, and analogues of 4-OH-OPB, colchicine, Ibuprofen, Naproxen, and acetyl

salicylic acid, or wherein 4-OH-OPB is administered to a subject with chronic infections or AIDS after removing the collocated infected cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 60 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for A method for stimulating clonal cell growth comprising: administering to cells an effective amount of a clonal mitotic stimulator, wherein the clonal mitotic stimulators comprise insulin, insulin like growth factors, conditioned medium, serum factors, Mito+, or Benzo(a)pyrene, *does not* reasonably provide enablement for a method for stimulating clonal cell growth comprising: administering to cells an effective amount of a clonal mitotic stimulator, wherein the clonal mitotic stimulators comprise, serum extenders, Diclofenak, Sulindak or Benzo(a)pyrene and analogues thereof or analogues of insulin, insulin like growth factors, conditioned medium, serum factors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4)

the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claims 48, 49, 51-53 are broadly drawn to a method for inhibiting clonal cell growth or clonal cell growth in a subject, comprising: administering to the cells or subject an effective amount of a clonal mitotic inhibitor , wherein the clonal mitotic inhibitors are selected from the group consisting of 4-OH-OPB, colchicine, Ibuprofen, Naproxen, Acetyl salicylic acid, p-hydroxy-azobenzene, 2-Butyl-2-hydroxy-N-(4- hydroxy-phenyl)-N'-phenyl malonamide, 1,2-diphenyl-4-hydroxy-4- [2-(phenylsulfinyl)ethyl]-3,5-pyrazolidinedione, and analogues thereof. The claims encompass inhibiting clonal cell growth in any cell type *in vitro* or *in vivo* with the claimed compounds and unlimited analogues thereof.

Claim 60 is broadly drawn to a method for stimulating clonal cell growth comprising: administering to cells an effective amount of a clonal mitotic stimulator, wherein the clonal mitotic stimulators comprise insulin, insulin like growth factors, conditioned medium, serum factors, serum extenders, Diclofenak, Sulindak or Benzo(a)pyrene and analogues thereof. The claim encompass stimulating clonal cell growth in any cell type *in vitro* or *in vivo* with the claimed compounds and unlimited analogues thereof

It is noted that although claims 48, 51, and 60 depend from independent claims that use the method of claims 28 to identify clonal mitotic inhibitors or stimulators, the inhibitors of claims 48, 51, and 60 were not identified by the method of claim 28 and do not necessarily have the properties of a clonal inhibitor or stimulator.

The specification teaches that 4-OH-OPB could inhibit the development of Ehrlich ascites tumors when injected with the tumor cells. See Experiment 8 and 9. The specification

teaches that 4-OH-OPB could inhibit the development of spleen antibody producing cells. See Experiment 10.

The specification teaches that 4-OH-OPB could inhibit the HSV viral production in culture. See Experiments 11 and 12.

The specification teaches that 4-OH-OPB inhibited the clonal growth of S100T1 cells in low density cell soft agar culture in and did not inhibit clonal cell growth in high density cultures. See Experiment 13- 25.

The specification teaches that colchicine inhibited the clonal growth of S100T1 cells in low density cell soft agar culture in and did not inhibit clonal cell growth in high density cultures. See Experiment 13, 15-18.

The specification teaches that diclofenac did not inhibit the clonal growth of S100T1 cells soft agar culture and may have shown slight stimulatory effect. See Experiment 15.

The specification teaches that ibuprofen, naproxen, and acetyl salicylic acid, inhibited the clonal growth of S100T1 cells soft agar culture. See Experiments 15 and16.

The specification teaches that 2-Butyl-N-(4-hydroxy-phenyl)-N'-phenylmalonamide did not strongly inhibit the clonal growth of S100T1 cells in high or low density cell soft agar culture. See Table 1, pages 31-32, and Experiment 22, 23, and 25.

The specification teaches that 1, 2-diphenyl-4-hydroxy-4-[2-(phenylsulfinyl)ethyl]-3,5-pyrazolidinedione did not strongly inhibit the clonal growth of S100T1 cells in high or low density cell soft agar culture. See Table 1, pages 31-32, and Experiment 22 and 25.

The specification teaches that p-hydroxy-azobenzene did not strongly inhibit the clonal growth of S100T1 cells in high or low density cell soft agar culture. See Table 1, pages 31-32, and Experiment 23 and 25.

The specification teaches that Benzo (a) pyrene weakly stimulated the clonal growth of S100T1 cells in low density cell soft agar culture. See Experiment 26.

The specification teaches that Sulindac had stimulatory and inhibitory effects on the clonal growth of S100T1 cells l soft agar culture. See experiment 26.

The specification teaches that the serum extender Mito+, insulin and conditioned medium stimulated growth in of BHK21/C13 cells in soft agar. See Experiment 3 and page 57.

One of skill in the art cannot extrapolate the teachings of the specification to enable the full scope of the claims to use all of the compounds claimed in claims 48, 51 and 60 clonal mitotic inhibitors and stimulators in any cell type under any condition because some of the claimed compounds have been only tested for their activity *in vitro* against one cultured cell type (S100T1). These effects cannot be predictably extrapolated to clonal inhibition or stimulation to any cell type under any condition because cultured cells can produce artifactual responses that are not reflective of the *in vivo* response of cells and cells are heterogeneous in the phenotypes and responses to drugs like clonal mitotic inhibitors or stimulators.

In particular as drawn to cell culture artifacts, the characteristics of cultured cell lines generally differ significantly from the characteristics of cells in a whole organism. As discussed in Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p. 4), it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-

dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, a petri dish cancer is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer further teaches that when a normal or malignant cell adapts to immortal life in culture, it takes an evolutionary-type step that enables the new line to thrive in its artificial environment and thus transforms a cell from one that is stable and differentiated to one that is not. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-cell and cell-cell interactions. Further, the art recognizes the problem of molecular artifacts associated with cell culture. For example, Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded. This is exemplified by the teachings of Zellner et al. (Clin. Can. Res., 1998, 4:1797-1802) who specifically teach that products are overexpressed in glioblastoma (GBM)-derived cell lines which are not overexpressed *in vivo*. More recently, Zips et al (In vivo, 2005, 19:1-7) specifically teaches that

despite their importance for drug testing, *in vitro* methods are beset by pitfalls and inherent limitations (p. 3, col. 1). In particular the authors state that "It is obvious that cells in culture represent an artificial and simplified system. Unlike the situation *in vitro,* a tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Vascularisation, perfusion and thereby, drug access to the tumor cells are not evenly distributed and in this fact consists an important source of heterogeneity in tumor response to drugs that does not exist *in vitro.* Therefore, prediction of drug effects in cancer patients based solely on *in vitro* data is not reliable and further evaluations in animal tumor systems is essential" (p. 3, col. 2). Additionally Clark et al. (US Pat. App. Pub. 2006/0019256, January 2006) teach that "[a]lthough cell lines have led to remarkable advances in our understanding of the molecular and biochemical changes in cancer cells, their use in the identification of effective cancer therapies is somewhat limited. Cell lines are imperfect predictors of drug efficacy in de novo tumors. Several factors likely account for this deficiency. Cancer cell lines are selected from a sub-population of cancer cells that are specifically adapted to growth in tissue culture and the biological and functional properties of these cell lines can change dramatically. Furthermore, cancer cells from only a minority of breast cancer tumors establish cell lines or xenograft tumors. The phenotypic and functional characteristics of these cell lines can change drastically relative to their properties in vivo. For example, the marker expression of both normal hematopoietic and leukemic tissue culture cells can change rapidly in tissue culture and often does not reflect that of the original stem cells from which they were derived. Even when conditions are devised to permit the proliferation of normal stem cells in culture, the conditions often promote self-renewal or differentiation in a way that prevents the stem cells in culture from recapitulating the

hierarchy of cell populations that exist in vivo. Taken together, these observations suggest that the biological properties of cell lines can differ markedly from the cancer cells from which they were derived. This likely explains at least in part why the cell lines often are poor predictors of a drug's efficacy in the clinic," see para. 0109. Thus, the unpredictability of extrapolating *in vitro* cell data to the *in vivo* situation is well known in the art.

In addition, clonal mitotic inhibitors or stimulators must accomplish several tasks to be effective *in vivo*. They must be delivered into the circulation that supplies the cells and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful delivery of these agents. The clonal mitotic inhibitors or stimulators may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half-life. In addition, the clonal mitotic inhibitors or stimulators may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where it has no effect, circulation into the target area may be insufficient to carry the clonal mitotic inhibitors or stimulators and a large enough local concentration may not be established.

Thus, based on the effects in the specification observed with a single cell line in vitro, one of skill in the art would not predictably expect that all of the claimed compounds or analogues thereof would inhibit or stimulate clonal growth in any cell type under any condition *in vivo* or *in vitro*. Thus, undue experimentation would be required to make and use the method as broadly claimed.

Additionally, as drawn to the heterogeneity of cell phenotypes, Busken, C. et al. (Digestive Disease Week Abstracts and Itinerary Planner, 2003, abstract No: 850), teach that there is a difference in COX-2 expression with respect to intensity, homogeneity, localization and prognostic significance between adenocarcinoma of the cardia and distal esophagus, suggesting that these two cancers have different etiology and genetic constitution (last five lines of the abstract). Additionally, Kaiser (Science, 2006, 313: 1370) teaches that in a genomic analysis of mutations in breast and colon cancers, it was found that the cancer genes differ between each colon and breast cancers and each tumor had a different pattern of mutations. Kaiser teaches that the steps to cancer may be more complex than had been anticipated, see 3rd col. Furthermore, Krontiris and Capizzi (Internal Medicine, 4th Edition, Editor-in-chief Jay Stein, Elsevier Science, 1994 Chapters 71-72, pages 699-729) teach that the various types of cancers have different causative agents, involve different cellular mechanisms, and, consequently, differ in treatment protocols. Chemotherapeutic agents are frequently useful against a specific type of neoplasm and especially with the unpredictability of the art there are no drugs broadly effective against all forms of cancer, see Carter, S. K. et al. (Chemotherapy of Cancer; Second edition; John Wiley & Sons : New York, 1981; appendix C). Additionally, USPN 6,258,845 (Gerner et al. July 10, 2001) teaches that sulindac inhibits colon carcinogenesis in a rat model by the induction of apoptosis. See Col. 1-lines 34-45. Thus, one of skill in the art would not expect that sulindac to be a clonal mitotic stimulator in all cell types treated with it. Furthermore, USPN 4,880, 742 (Hayaishi et al. 1989) teach that Diclofenac inhibits the growth of T-cells with the AIDS virus. See Fig. 1 and 2 and claim 1. Thus, one of skill in the art would not expect that Diclofenac to be a clonal mitotic stimulator in all cell types treated with it.

Given the above, one of skill in the art would not predictably be able inhibit or stimulate clonal growth in any cell type under any condition with the all of claimed compounds and analogs thereof without undue experimentation.

Additionally as drawn to claim 55 wherein 4-OH-OPB is administered to a subject with chronic infections or AIDS after removing the collocated infected cells, one of skill in the art would not predictably expect to remove the collocated infected cells because HIV and the herpes simplex viruses form latent infections in cells that are not removed from the subject by treatments for these diseases used at the time the invention was made. In particular, Dybul et al. (MMWR Recommendations and Reports May 17, 2002, p.1-71) teach that eradication of HIV infection cannot be achieved with available anti-retroviral regimens, because the pool of latently infected CD4+ T cells is established early during infection and persists with a long half-life. See p. 13. Additionally, Efstathiou and Preston (Virus Res. 2005, 111:108-119) teach that a key characteristic of all herpes viruses is their ability to establish life-long latency within the infected host. See p. 108. Additionally, Smith et al. (Antiviral Res. 2001 52:19-24) teach that herpes simplex virus drugs like acyclovir have no effect on the latent HSV infection once established. See ¶ bridging p. 20 and 21 and p. 23. Thus, given the resistance of latent HIV and HSV infections to anti-viral treatments known at the time the invention was made, one of skill in the art would not be able to remove the collocated infected cells with methods known in the art or taught in the specification without undue experimentation.

The specification provides insufficient guidance with regard to these issues and provides insufficient working examples which would provide guidance to one skilled in the art and insufficient evidence has been provided which would allow one of skill in the art to predict that

the invention will function as claimed with a reasonable expectation of success. For the above reasons, undue experimentation would be required to practice the claimed invention.

10. 48, 49, 51-53 and 60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 48, 49, 51-53 are broadly drawn to a method for inhibiting clonal cell growth or clonal cell growth in a subject, comprising: administering to the cells or subject an effective amount of a clonal mitotic inhibitor , wherein the clonal mitotic inhibitors are selected from the group consisting of 4-OH-OPB, colchicine, Ibuprofen, Naproxen, Acetyl salicylic acid, p-hydroxy-azobenzene, 2-Butyl-2-hydroxy-N-(4- hydroxy-phenyl)-N'-phenyl malonamide, 1,2-diphenyl-4-hydroxy-4- [2-(phenylsulfinyl)ethyl]-3,5-pyrazolidinedione, and analogues thereof.

Claim 60 is broadly drawn to a method for stimulating clonal cell growth comprising: administering to cells an effective amount of a clonal mitotic stimulator, wherein the clonal mitotic stimulators comprise insulin, insulin like growth factors, conditioned medium, serum factors, serum extenders, Diclofenak, Sulindak or Benzo(a)pyrene and analogues thereof.

The specification does not put any limit on the analogues of the claimed compounds. Thus, the instant method claims are reliant on the identity of a large genus of analogues to inhibit or stimulate clonal cell growth. When given the broadest reasonable interpretation, the term "analogues" encompasses any type of compound with little or not structural similarity to the

claimed compounds, which can inhibit or stimulate clonal cell growth. The description of the various claimed compounds fails to adequately describe the genus of analogues because said genus tolerates members which differ significantly in both structure and function from that of the claimed compounds. One of skill in the art can reasonably conclude that applicant was not in possession of a genus of "analogues" of the claimed compounds at the time the invention was filed. Because the genus of "analogues" is not adequately described, the method claims relying on said genus are also not adequately described.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of analogues of the claimed compounds, per Lilly by structurally describing a representative number of analogues of the claimed compound, or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe analogues of the claimed compounds, in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide any functional characteristics coupled with a known or disclosed correlation between structure and function for analogues of the claimed compounds. Although the specification discloses the claimed compounds, this does not provide an adequate description of analogues of the claimed compounds that would satisfy the standard set out in Enzo.

The specification also fails to describe analogues of the claimed compounds by the test set out in Lilly. The specification describes only the claimed compounds a few related compounds. Therefore, it necessarily fails to describe a "representative number" of species of analogues of the claimed compounds. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of analogues of the claimed compounds that is required to practice the claimed invention or reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the broadly claimed invention.

11. Claims 54-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The limitations of "wherein 4-OH-OPB is administered to a subject after said subject has been exposed or infected to HIV and before HIV infected cells are piling up", "wherein 4-OH-OPB is administered to a subject with chronic infections or AIDS after removing the collocated infected cells", and "wherein 4-OH-OPB is administered in combination with an anti-viral treatment to inhibit drug resistance" claimed in Claims 54-56 have no clear support in the specification and the claims as originally filed. Applicants pointed Examples 10-12 in the Remarks of 01/11/2008 for support of claims 54-56. A review of the specification discloses support for testing the effect of 4-OH-OPB on the number of cells in spleen with production of antibodies against sheep red cells after immunization (Experiment 10); testing herpes virus type 1 for sensitivity to 4-OH-OPB (Experiment 11); and testing herpes virus type 2 for sensitivity to 4-OH-OPB (Experiment 12). The suggested support is not found persuasive because there is nothing in the specification to suggest the specific treatments claimed in claims 54-56. The subject matter claimed in claims 54-56 broadens the scope of the invention as originally disclosed in the specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 47-54, 56, 57, 59 and 60 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 01/00585 (Tjotta et al. 4 January 2001, IDS) evidenced by Szucs et al. (Bulletin World Health Org. 1988 66: 729-737).

It is noted that the clonal mitotic inhibitor of claims 47, 50 and 59 are products identified by a process and the patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claim. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). Thus, the clonal mitotic inhibitor used in claims 47, 50 and 59 need not be selected by the method of claim 28.

WO 01/00585 (Tjotta et al. 4 January 2001) teach inhibition of T-lymphocyte growth, T-cell tumor growth and Kaposi's sarcoma with pyrazolidinols, including 4-OH-OPB. WO 01/00585 teaches treating subjects with HIV and Herpes infection with 4-OH-OPB, Which would be before HIV infected cells are piling up given the undefined time before HIV infected cells are piling up. See Abstract, pages 1-10, and claims 1-12. WO 01/00585 teaches administering additional antiviral agents with 4-OH-OPB to inhibit drug resistance. See claim 5 and ¶ bridging p. 5and 6. WO 01/00585 teaches adding fresh growth media to MT-4 cells, Additionally, Szucs et al. teach that MT-4 are grown in serum. See p. 730-1st col. Thus, one of skill in the art would immediately recognize that MT-4 cells are grown in serum. See Example

12. Although, WO 01/00585 does not specifically teach that T-lymphocyte growth and Kaposi's sarcoma is clonal cell growth, in the absence of a limiting definition of clonal cell growth, WO 01/00585 anticipates the claims.

Although the reference does not specifically state that 4-OH-OPB was administered as an initial treatment in order to inhibit metastasis of a cancer, the claimed method appears to be the same as the prior art product, absent a showing of unobvious differences as the administered 4-OH-OPB would inherently have this property . The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the method of the prior art does not possess the same material, structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from those taught by the prior art and to establish patentable differences. See *In re Best* 562F.2d 1252, 195 USPQ 430 (CCPA 1977).

13. Claims 47-53, 56, 57, 59 and 60 are rejected under 35 U.S.C. 102(b) as being anticipated by USPN 6,258,845 (Gerner et al. July 10, 2001).

It is noted that the clonal mitotic inhibitor of claims 47, 50 and 59 are products identified by a process and the patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claim. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). Thus, the clonal mitotic inhibitor used in claims 47, 50 and 59 need not be selected by the method of claim 28.

USPN 6,258,845 treating cells and subjects with acetyl salicylic acid (aspirin), ibuprofen, and sulindac for the treatment of cancer. See claims, col. 1, col. 5-lines 40-66, col. 8-line 50 to col. 10-line 20, Figs. 1-8, Examples 1-6. USPN 6,258,845 teaches culturing caco-2 in fetal

bovine serum and sulindac and performing clonogenic assays. See Example 1 and Fig. 1-4. It is noted that all individuals have at least some level of risk for the conditions of claim 52 and 53, thus these individuals would be treated by the methods of USPN 6,258,845. Given that acetyl salicylic acid (aspirin), ibuprofen, and sulindac are used for the treatment of cancer they would be administer at amounts effective to inhibit clonal cell growth.

14. Claims 47-53, 56, 57, 59 and 60 are rejected under 35 U.S.C. 102(b) as being anticipated by USPN 4,880,742 (Hayaishi et al. 1989) evidenced by McClain et al. (FASEB Journal, 1995 9: 1345-1354).

It is noted that the clonal mitotic inhibitor of claims 47, 50 and 59 are products identified by a process and the patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claim. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). Thus, the clonal mitotic inhibitor used in claims 47, 50 and 59 need not be selected by the method of claim 28.

USPN 4,880,742 teaches treating Molt-4 leukemia cells with Diclofenac, which is encompassed by "analogues" in claims 48 and 51 in amounts effective to kill the cells, which would inhibit their clonal cell growth. See Example 6, Fig. 1 and 2, and claim 1. USPN 4,880,742 also teaches treating with effective amounts of aspirin (acetyl salicylic acid), naproxen, sulindac, and ibuprofen for therapy. See Col. 1-4.

McClain et al. (FASEB Journal, 1995 9: 1345-1354) teach that MolT-4 cells are grown in fetal bovine serum. See p. 1346-1st col. Thus, one of skill in the art would have inherently

recognized that the Molt-4 cells of USPN 4,880,742 are grown in serum to stimulate clonal cell growth.

15. Claims 47, 48, 59 and 60 are rejected under 35 U.S.C. 102(b) as being anticipated by De Asua et al. (Proc. Natl. Acad. Sci USA, 1973, 70: 1388-13920, previously cited).

It is noted that the clonal mitotic inhibitor of claims 47 and 59 are products identified by a process and the patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claim. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). Thus, the clonal mitotic inhibitor used in 47 and 59 need not be selected by the method of claim 28.

De Asua et al. teach stimulating the clonal growth of BHK21/13 cells with serum and insulin and inhibiting clonal growth with cAMP, which would be encompassed by the broadly claimed analogue. See p. 1388- 2nd col., p. 1389. Fig. 1-5.

16. Claims 47, 48, 59 and 60 are rejected under 35 U.S.C. 102(b) as being anticipated by Kamei H. (Cell Biol. Int. Rep. Jan. 1987, 11 (1): 35-41, previously cited).

It is noted that the clonal mitotic inhibitor of claims 47 and 59 are products identified by a process and the patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claim. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). Thus, the clonal mitotic inhibitor used in 47 and 59 need not be selected by the method of claim 28.

Kamei teaches stimulating the clonal growth of BHK21/13 cells with serum and insulin and inhibiting clonal growth with retinoic acid, which would be encompassed by the broadly claimed analogue. See p. 35, 36., Table 1 and 2, Fig. 1 and 2.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

17. Claim 58 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/00585 (Tjotta et al. 4 January 2001, IDS) in view of Tannock, I.F. (*Experimental Chemotherapy*, Ch. 19-p. 338 and 352-359, in The Basic Science Of Oncology Tannock and Hill, eds., New York 1992).

WO 01/00585 teaches as set forth above, but does not teach administering 4-OH-OPB to a subject undergoing conventional cancer treatment.

Tannock teaches that it has become common practice to treat cancer patients with multiple anti-cancer agents to enhance the tumor response over that of the individual agents. See p. 352-2nd col.., p. 353-1st col., p. 357- 2nd col. and Table 19.3. Tannock teaches that improvements in clinical chemotherapy have depended largely on the use of drugs in combination. See p. 338.

It would have been *prima facie* at the time the invention was made to combine the treatment of T-cell tumors and Kaposi's sarcoma with 4-OH-OPB with conventional cancer treatment because Tannock teaches that it is common practice to treat cancer patients with multiple anti-cancer agents to get an enhanced anti-tumor response. One of skill in the art would have been motivated to find the optimal treatment for cancers like T-cell tumors and Kaposi's sarcoma by combining the 4-OH-OPB treatment with conventional chemotherapy. Given that that the claimed compounds were known in the art for cancer treatment, one of skill in the art would have had a reasonable expectation of success of using the compounds in combination.

18. All other rejections and objections set forth in the Office Action of September 17, 2008 are withdrawn.

19. Claim 28, 30-34, 37-41, 44, and 46-61 are rejected.

20. Claims 42, 43, and 45 are objected to as being dependent upon a rejected base claim.

21. No claims allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571)272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Helms Larry can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Peter J Reddig/
Primary Examiner, Art Unit 1642